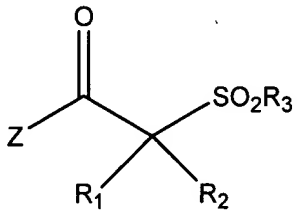
Listing of Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application.

1. **(Previously presented)** A method of preparing alpha-sulfonyl derivatives of the formula V:



V

wherein Z is H, OH, -NYOX, $-OR_5$ or $-NR_5R_6$;

X is hydrogen, alkyl of 1-6 carbon atoms, benzyl, hydroxyethyl, t-butyldimethylsilyl, trimethylsilyl or tetrahydropyranyl;

Y is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6 to 10 carbon atoms, 5-10 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O and S, cycloalkyl of 3-6 carbon atoms, 5-10 membered cycloheteroalkyl; wherein said alkyl, aryl, heteroaryl, cycloalkyl and cycloheteroalkyl group of Y is optionally substituted on any atom capable of substitution, with 1 to 3 substituents selected from the group consisting of halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, $-OR_5$, =O, -CN, $-COR_5$, perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbon atoms, $-CONR_5R_6$,$-S(O)_nR_5$, $-OPO(OR_5)OR_6$, $-PO(OR_5)R_6$, $-OC(O)OR_5$, $-OR_5NR_5R_6$, $-OC(O)NR_5R_6$, $-C(O)NR_5OR_6$, $-COOR_5$, $-SO_3H$, $-NR_5R_6$, $-N[(CH_2)_2]_2NR_5$, $-NR_5COR_6$, $-NR_5COOR_6$, $SO_2NR_5R_6$, $-NO_2$, $-N(R_5)SO_2R_6$, $-NR_5CONR_5R_6$, $-NR_5C(=NR_6)NR_5R_6$, $-NR_5C(=NR_6)N(SO_2R_5)R_6$, $-NR_5C(=NR_6)NR_6)N(C=OR_5)R_6$, -

tetrazol-5-yl, $-SO_2NHCN$, $-SO_2NHCONR_5R_6$, phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

R_1 and R_2 taken together with the carbon atom to which they are attached form a cycloalkyl ring of 3-8 carbon atoms or a 5-10 membered cycloheteroalkyl ring containing 1-3 heteroatoms selected from the group consisting of N, NR_4, O and S; and the cycloheteroalkyl may be optionally substituted on any atom capable of substitution with from 1 to 3 substituents selected from halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, $-OR_5$, =O, -CN, $-COR_5$, perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbons atoms, $-CONR_2R_6$, $-S(O)_nR_5$, $-OPO(OR_5)OR_6$, $-PO(OR_5)R_6$, $-OC(O)OR_5$, $-OR_5NR_5R_6$, $-OC(O)NR_5R_6$, $-C(O)NR_5OR_6$, $-COOR_5$, $-SO_3H$, $-NR_5R_6$, $-N[(CH_2)_2]_2NR_5$, $-NR_5COR_6$, $-NR_5COOR_6$, $SO_2NR_5R_6$, $-NO_2$, $-N(R_5)SO_2R_6$, $-NR_5CONR_5R_6$, $-NR_5C(=NR_6)NR_5R_6$, $-NR_5C(=NR_6)N(SO_2R_5)R_6$, $-NR_5C(=NR_6)N(C=OR_5)R_6$, -tetrazol-5-yl, $-SO_2NHCN$, $-SO_2NHCONR_5R_6$, phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

R_3 is alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms having 1 to 3 double bonds, alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, 5-10 membered cycloheteroalkyl, aryl of 6 to 10 carbon atoms, 5-6 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O, and S; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl of R_3 may optionally be substituted on any atom cable of substitution with from 1 to 3 substituents selected from halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds, alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, $-OR_5$, =O, -CN, $-COR_5$, perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbon atoms, $-CONR_5R_6$, $-S(O)_nR_5$, -

$OPO(OR_5)OR_6$, $-PO(OR_5)R_6$, $-OC(O)OR_5$, $-OR_5NR_5R_6$, $-OC(O)NR_5R_6$, $-C(O)NR_5OR_6$, $-COOR_5$, $-SO_3H$, $-NR_5R_6$, $-N[(CH_2)_2]_2NR_5$, $-NR_5COR_6$, $-NR_5COOR_6$, $SO_2NR_5R_6$, $-NO_2$, $-N(R_5)SO_2R_6$, $-NR_5CONR_5R_6$, $-NR_5C(=NR_6)NR_5R_6$, $-NR_5C(=NR_6)N(SO_2R_5)R_6$, $-NR_5C(=NR_6)N(C=OR_5)R_6$, -tetrazol-5-yl, SO_2NHCN, $-SO_2NHCONR_5R_6$, phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

R_4 is hydrogen; aryl; aralkyl, heteroaryl; heteroaralkyl, alkyl of 1-6 carbon atoms; cycloalkyl of 3-6 carbon atoms; $-C(O)_nR_5$, $-CONR_5R_6$, or SO_2R_5;

R_5 and R_6 are each independently hydrogen, optionally substituted aryl; 4-8 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O and S; cycloalkyl of 3-6 carbon atoms; 5-10 membered cycloheteroalkyl; alkyl of 1-18 carbon atoms; alkenyl of 2-18 carbon atoms or alkynyl of 2-18 carbon atoms; or R_5 and R_6 taken together with the nitrogen atom to which they are attached may form a 5-10 membered cycloheteroalkyl ring; and

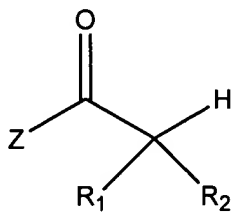
n is 1 or 2; or a pharmaceutical salt thereof,

which comprises reacting a sulfonyl fluoride of the formula III

$$R_3'SO_2F$$

III

wherein R_3' is as hereinabove defined for R_3 with the proviso that R_3' does not contain a group that can form an anion under basic conditions; with a carbonyl compound of the formula IV:

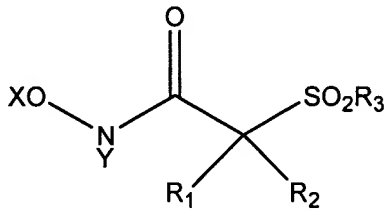


IV

wherein Z is H, OH, YNOX, $-NR_5R_6$ or OR_5, and X, Y, R_1, R_2, R_5, and R_6 are as hereinabove defined; in the presence of a metal hydride or amide base in an ether organic solvent at temperatures from about -78°C to about 30°C to produce an alpha-sulfonyl carbonyl compound of formula V;

any reactive substituent group(s) being protected during the reaction and removed thereafter; and further if desired isolating any chiral or stereoisomeric product as an individual isomer.

2. **(Previously presented)** The method as claimed in claim 1 in which the compound of formula (V) prepared wherein Z is H, OH, $-NR_5R_6$ or OR_5 is further reacted to convert it to an alpha-sulfonyl hydroxamic acid derivative of the formula I:



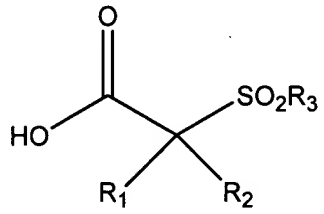
I

wherein X, Y, R_1, R_2 and R_3 are as defined in claim 1 or a pharmaceutically acceptable salt thereof; any reactive substituent group(s) being protected during the reaction and removed thereafter; and further if desired isolating any chiral or stereoisomeric product as an individual isomer.

3. **(Previously presented)** The method as claimed in Claim 2 wherein Z in the compound of formula V prepared is:

OR_5 wherein R_5 is other than hydrogen and the conversion to the alpha-sulfonyl hydroxamic acid derivative of the formula I is carried out by:

reacting the compound of formula V with an alkali metal hydroxide in the presence of water, and/or ether organic solvent or alcohol at temperatures ranging from about 0°C to about 100°C to produce a carboxylic acid of the formula VI:



VI

wherein, R_1, R_2, and R_3 are as hereinabove defined; and

reacting the carboxylic acid of formula VI with a hydroxylamine or hydroxylamine derivative of the formula VII:

XONHY

VII

wherein X and Y are as hereinabove defined; in the presence of suitable coupling reagent and polar organic solvent to produce a hydroxamate of the formula I

or

OH and the conversion to the alpha-sulfonyl hydroxamic acid derivative of the formula I is carried out according to step b) above.

4. **(Previously presented)** The method of Claim 3 wherein the ether organic solvent in step a) is selected from the group consisting of tetrahydrofuran, diethylether and dioxane.

5. **(Previously presented)** The method of Claim 3 wherein the alcohol in step a) is selected from the group consisting of methanol and ethanol.

6. **(Previously presented)** The method of Claim 3 wherein the alkali metal hydroxide in step a) is selected from the group consisting of lithium hydroxide and sodium hydroxide.

7. **(Original)** The method of Claim 3 wherein the polar organic solvent in step b) is dimethylformamide.

8. **(Previously presented)** The method of Claim 3 wherein the coupling reagent is selected from the group consisting of 1-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride, N-hydroxybenzotriazole, N-methylmorpholine oxalylchloride and triethylamine.

9. **(Original)** The method of Claim 3 wherein the coupling reaction is carried out at a temperature from about 0°C to 30°C.

10. **(Previously presented)** The method of Claim 3 wherein the ether organic solvent used in the reaction between the compounds of formula III and IV is selected from the group consisting of tetrahydrofuran, diethylether and dioxane.

11. **(Previously presented)** The method of Claim 3 wherein the metal hydride base or amide base used in the reaction between the compounds of formula III and IV and is selected from the group consisting of lithium diisopropylamine, lithiumhexamethyldisilazide, and sodium hydride.

12. **(Original)** The method of Claim 1 wherein the sulfonyl fluoride of formula III is prepared by reacting a sulfonyl chloride of the formula II

$$R_3'SO_2Cl$$

II

wherein R_3' is as defined for R_3 in claim 1 with the proviso that R_3' does not contain a group that can form an anion under basic conditions, with a fluorinating agent in the presence of a polar organic solvent from about 15°C to about 30°C.

13. **(Previously presented)** The method of Claim 12 wherein the fluorinating agent is selected from the group consisting of potassium fluoride, potassium fluoride-calcium fluoride mixture and cesium fluoride.

14. **(Previously presented)** The method of Claim 12 wherein the polar organic solvent is selected from the group consisting of acetonitrile and tetrahydrofuran.

15 – 28. **(Canceled)**

29. **(Original)** The method of Claim 1 wherein X is H or lower alkyl of 1-6 carbon atoms.

30. **(Original)** The method of Claim 1 wherein Y is H.

31. **(Original)** The method of Claim 1 where Z is OH or OR_5 where R_5 is C_1-C_6 alkyl.

32. **(Canceled)**

33. **(Previously presented)** The method of Claim 1 wherein the cycloheteroalkyl ring is saturated.

34. **(Previously presented)** The method of Claim 1 wherein the cycloheteroalkyl ring is has 6 atoms.

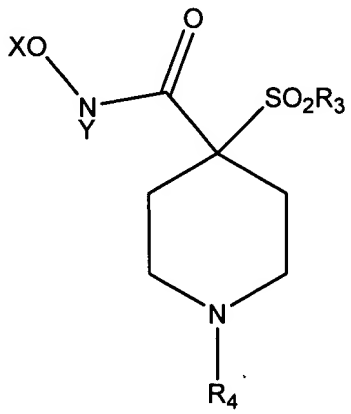
35. **(Previously presented)** The method of Claim 1 wherein the heteroatom is NR_4 and R_4 is hydrogen, trifluoromethylsulfonyl, optionally substituted aralkyl of 7-10 carbon atoms, (C_6-C_{10}-aryl)carbonyl-, cycloheteroalkyl-carbonyl or heteroaryl-carbonyl.

36. **(Original)** The method of Claim 1 wherein R_3 is an optionally substituted C_6-C_{10} aryl group.

37. **(Original)** The method of Claim 1 wherein R_3 is a phenyl group substituted by one or more OR_5 groups.

38. **(Original)** The method of Claim 1 wherein R_5 is C_1- C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or halophenyl.

39. **(Previously presented)** The method of Claim 1 in which the compound prepared is an alpha-sulfonyl hydroxamic acid derivatives of the general formula IA:



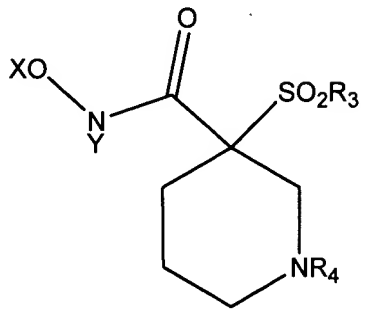
IA

wherein

X is hydrogen, or alkyl of 1-6 carbon atoms; and Y, R_3 and R_4 are as defined in Claim 1 or a pharmaceutically acceptable salt thereof.

40-44. **(Canceled)**

45. **(Original)** A compound of Formula IX



IX

wherein

X is hydrogen, or alkyl of 1-6 carbon atoms;

Y is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6 to 10 carbon atoms, 5-10 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O and S, cycloalkyl of 3-6 carbon atoms, 5-10 membered cycloheteroalkyl; wherein said alkyl, aryl, heteroaryl, cycloalkyl and cycloheteroalkyl group of Y is optionally substituted on any atom capable of substitution, with 1 to 3 substituents selected from the group consisting of halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, $-OR_5$, =O, -CN, $-COR_5$, perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbon atoms, $-CONR_5R_6$, $-S(O)_nR_5$, -

$OPO(OR_5)OR_6$, $-PO(OR_5)R_6$, $-OC(O)OR_5$, $-OR_5NR_5R_6$, $-OC(O)NR_5R_6$, $-C(O)NR_5OR_6$, $-COOR_5$, $-SO_3H$, $-NR_5R_6$, $-N[(CH_2)_2]_2NR_5$, $-NR_5COR_6$, $-NR_5COOR_6$, $SO_2NR_5R_6$, $-NO_2$, $-N(R_5)SO_2R_6$, $-NR_5CONR_5R_6$, $-NR_5C(=NR_6)NR_5R_6$, $-NR_5C(=NR_6)N(SO_2R_5)R_6$, $-NR_5C(=NR_6)N(C=OR_5)R_6$, -tetrazol-5-yl, $-SO_2NHCN$, $-SO_2NHCONR_5R_6$, phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

R_3 is alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms having 1 to 3 double bonds, alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, 5-10 membered cycloheteroalkyl, aryl of 6 to 10 carbon atoms, 5-6 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O, and S;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl of R_3 may optionally be substituted on any atom capable of substitution with from 1 to 3 substituents selected from halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, $-OR_5$, =O, -CN, $-COR_5$, perfluoroalkyl of 1-4 carbon atoms, -O-perfluororalkyl of 1-4 carbon atoms, $-CONR_5R_6$, $-S(O)_nR_5$, $-OPO(OR_5)OR_6$, $-PO(OR_5)R_6$, $-OC(O)OR_5$, $-OR_5NR_5R_6$, $-OC(O)NR_5R_6$, $-C(O)NR_5OR_6$, $-COOR_5$, $-SO_3H$, $-NR_5R_6$, $-N[(CH_2)_2]_2NR_5$, $-NR_5COR_6$, $-NR_5COOR_6$, $SO_2NR_5R_6$, $-NO_2$, $-N(R_5)SO_2R_6$, $-NR_5CONR_5R_6$, $-NR_5C(=NR_6)NR_5R_6$, $-NR_5C(=NR_6)N(SO_2R_5)R_6$, $-NR_5C(=NR_6)N(C=OR_5)R_6$, -tetrazol-5-yl, $-SO_2NHCN$, $-SO_2NHCONR_5R_6$, phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

R_3 is alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms having 1 to 3 double bonds, alkynyl of 2-18 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, 5-10 membered cycloheteroalkyl, aryl of 6 to 10 carbon atoms, 5-6 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O, and S;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloheteroalkyl, aryl and heteroaryl of R_3 may optionally be substituted on any atom capable of substitution with from 1 to 3 substituents

selected from halogen, alkyl of 1-6 carbon atoms; alkenyl of 2-6 carbon atoms having from 1 to 3 double bonds; alkynyl of 2-6 carbon atoms having from 1 to 3 triple bonds, cycloalkyl of 3-6 carbon atoms, $-OR_5$, =O, -CN, $-COR_5$, perfluoroalkyl of 1-4 carbon atoms, -O-perfluoroalkyl of 1-4 carbon atoms, $-CONR_5R_6$, $-S(O)_nR_5$, $-OPO(OR_5)OR_6$, $-PO(OR_5)R_6$, $-OC(O)OR_5$, $-OR_5NR_5R_6$, $-OC(O)NR_5R_6$, $-C(O)NR_5OR_6$, $-COOR_5$, $-SO_3H$, $-NR_5R_6$, $-N[(CH_2)_2]_2NR_5$, $-NR_5COR_6$, $-NR_5COOR_6$, $SO_2NR_5R_6$, $-NO_2$, $-N(R_5)SO_2R_6$, $-NR_5CONR_5R_6$, $-NR_5C(=NR_6)NR_5R_6$, $-NR_5C(-NR_6)N(SO_2R_5)R_6$, $-NR_5C(=NR_6)N(C=OR_5)R_6$, tetrazol-5-yl, $-SO_2NHCN$, $-SO_2NHCONR_5R_6$, phenyl, heteroaryl and 5-10 membered cycloheteroalkyl;

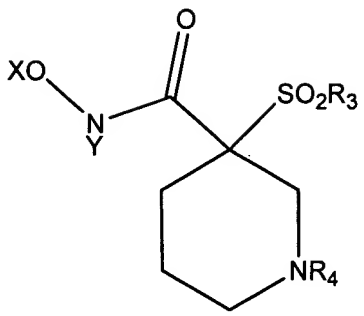
R_4 is hydrogen; aryl; aralkyl, heteroaryl; heteroaralkyl, alkyl of 1-6 carbon atoms; cycloalkyl of 3-6 carbon atoms; $-C(O)_nR_5$, $CONR_5R_6$ or SO_2R_5;

R_5 and R_6 are each independently hydrogen, optionally substituted aryl; 4-8 membered heteroaryl having 1-3 heteroatoms selected from N, NR_4, O and S; cycloalkyl of 3-6 carbon atoms; 5-10 membered cycloheteroalkyl; alkyl of 1-18 carbon atoms; alkenyl of 2-18 carbon atoms or alkynyl of 2-18 carbon atoms; or R_5 and R_6 taken together with the nitrogen atom to which they are attached may form a 5-10 membered cycloheteroalkyl ring; and

n is 1 or 2; or an optical isomer thereof or a pharmaceutically acceptable salt thereof.

46. **(Previously presented)** The compound according to Claim 45 which is 1-benzyl-3-(4-methoxy-benzenesulfonyl)piperidine-3-carboxylic acid hydroxamide.

47. **(Original)** A pharmaceutical composition comprising a compound of Formula IX.



IX

as defined in claim 45 or claim 46 or a pharmaceutically acceptable salt thereof;

and a pharmaceutically acceptable carrier.

48. **(Original)** A method of inhibiting pathological changes mediated by TNF-alpha converting enzymes (TACE) in a mammal in need thereof which comprises administering to said mammal a therapeutically effective amount of a compound of Claim 45, or a pharmaceutically acceptable salt thereof.

49. **(Original)** The method of Claim 48 wherein the condition treated is rheumatoid arthritis, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease or HIV infection.

50-52. **(Canceled)**

53. **(Previously presented)** The method according to claim 38 wherein R_5 is C_1-C_6 alkyl substituted by C_2-C_6 alkynyl.